IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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| Applicant(s) | : Richard R. Bott et al. |
| Serial No. | : 10/576,356 |
| Filed | : December 11, 2006 |
| Title | : **PREPARATIONS FOR TOPICAL APPLICATION AND METHODS OF DELIVERING AN ACTIVE AGENT TO A SUBSTRATE** |
| Docket | : DOG 0101 PA/35319.68 |
| Art Unit | : 1611 |
| Examiner | : H. S. Park |
| Conf. No. | : 9374 |

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**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

## BRIEF ON APPEAL

This is an appeal from the Office Action mailed April 7, 2011, finally rejecting claims 72 and 74-91, all of the claims presently pending in the application. A Notice of Appeal was timely filed on September 6, 2011, with a two-month extension of time and the accompanying fees.

A Request for a one-month extension of time in which to file the brief accompanies this paper. An authorization to charge our credit card in the amount of $770.00 accompanies this Brief in accordance with 37 CFR §41.20(b)(2) and 37 CFR §1.17(a).

### Real Parties in Interest

The real parties in interest in this application are Danisco US, Inc., by change of name from Genencor International, Inc., and Dow Corning Corporation, by assignments from the named inventors. The assignments were recorded in the files of the U.S. Patent and Trademark Office on October 27, 2006, at Reel 018446 and Frames 0624 and 0592, respectively.

**Related Appeals and Interferences**

Appellants know of no currently pending related appeals or interferences that would have an effect on the outcome of this appeal.

**Status of Claims**

Claims 72 and 74-91 are currently pending in this application and are before this Board for consideration on appeal. A copy of the appealed claims is found in the Appendix attached to this brief.

**Status of Amendments**

All of the amendments previously filed in this application have been entered.

**Summary of Claimed Subject Matter**

The following is a concise explanation of the subject matter defined in each of the independent claims and each of the dependent claims argued separately. Reference to the drawing figures and specifically depicted embodiments of the invention are for the convenience of the Board and are not to be interpreted as limitations on the claims.

Claim 72

Claim 72 is directed to a controlled-release composition for topical application to a substrate (page 5, lines 3-5). The composition comprises an oil-in-water emulsion substantially free of lipophilic solvent (page 6, lines 5-9) wherein the oil-in-water emulsion has a hydrophilic phase comprising a protein as an active agent (page 11, lines 22-27), water, and a carrier (page 11, lines 14-17), and a hydrophobic phase comprising a silicone component (page 6, lines 15-18).

Claim 87

Claim 87 depends from claim 72 and recites that the controlled release composition is in the form of a multi-layer dressing (see, Figs. 1A through 1D) for topical

application to a substrate, the dressing including: (A) a controlled-release layer ("controlled release composition layer" in Figs. 1A through 1C) formed from the controlled-release composition of claim 72; (B) an adhesive layer ("adhesive layer" in Figs. 1A through 1D) disposed adjacent to the controlled-release layer for adhering the dressing to the substrate; and (C) an additional layer selected from the group of a backing layer, a cushioning layer, an absorbent layer, a second adhesive layer, and combinations thereof ( page 18, lines 26-29; "backing layer" in Figs. 1A through 1D; "cushion layer" and "absorbent layer" in Fig. 1C.; and "outer ring of adhesive" in Fig. 1D).

Claim 88

Claim 88 depends from claim 87 and recites that the controlled-release layer is adjacent the substrate (Figs. 1B through 1D) and the additional layer is disposed adjacent to the adhesive layer and spaced from the controlled-release layer (Figs. 1A through 1D).

Claim 89

Claim 89 depends from claim 87 and recites that the controlled-release layer is dry in the dressing such that the controlled-release layer is free of water after the controlled-release layer is formed by the controlled-release composition (page 17, lines 29-30, and page 18, lines 1-2).

Claim 90

Claim 90 recites a method of delivering the controlled release composition as set forth in independent claim 72 to a substrate including:

applying the controlled release composition to a dressing (page 17, lines 25-29); and

applying the dressing to the substrate (page 4, lines 14-16).

**Grounds of Rejection to be Reviewed on Appeal**

The sole ground of rejection for review on appeal is:

Claims 72 and 74-91 stand rejected under 35 USC §103(a) as unpatentable over Kosal (US 6545086) in view of Bott et al. (US 2003/0180281) and Woodard et al. (US 4655767).

**ARGUMENT**

Rejection under 35 USC. §103(a) as being unpatentable over Kosal (US 6545086) in view of Bott et al. (US 2003/0180281) and Woodard et al. (US 4655767)

Claim 72 as representative of claims 72 and 74-86

To establish a prima facie case of obviousness, the Examiner must show, by reasoning or evidence, that: 1) there is some teaching, suggestion or motivation, either in the references themselves or in the knowledge available to one skilled in the art, to modify or combine the teachings of the references; 2) there is a reasonable expectation on the part of the skilled practitioner that the modification or combination will be successful; and 3) the prior art references teach or suggest all of the claim limitations. See MPEP §2143 and *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 167 L.Ed.2d 705, 82 USPQ2d 1385 (2007).

The invention itself, as delineated in the claims, may not be used as a template to find separate, individual elements in the prior art, and then to combine the elements and pronounce the combination obvious. The United States Supreme Court addressed the proper standards to combine references under 35 USC §103 in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 167 L.Ed.2d 705, 82 USPQ2d 1385 (2007). The Court, while disapproving a strict application of the Federal Circuit's "TSM" (teaching, suggestion or motivation) test for determining whether it would have been obvious to combine references under 35 USC §103, adopted an objective standard in which all of the facts and circumstances associated with the invention and the prior art are considered. In point of fact, the Supreme Court cited with approval Federal Circuit

cases adopting a more flexible TSM standard, and reaffirmed the standards for obviousness set out in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966). Judged in this light, the claimed subject matter cannot be said to be an obvious combination of the teachings of the references.

Appellants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness with respect to the applied prior art references for the reasons presented below.

(1) ***The primary reference is not directed to controlled delivery of a protein active, and the secondary reference is directed to a water-in-oil emulsion, unlike both the claimed composition and that of the primary reference.***

Kosal, the primary reference, is directed to silicone pressure sensitive adhesive compositions which comprise a disperse silicone phase in a continuous aqueous phase, i.e., an oil-in-water emulsion. Kosal lists a number of different possible uses for the adhesive including

> "paper coatings, such as adhesive labels and sealing strips, in adhesive modifiers such as release modifying additives for organic pressure sensitive adhesives, in personal care applications to give greater durability, protective qualities, water resistance and barrier properties, for example in eye cosmetics such as mascara and in sunscreen formulations as described in U.S. Pat. No. 5,451,610, and in medical applications such as transdermal drug delivery patches, described for example in U.S. Pat. No. 5,162,410, or to hold an active material such as a fungicide to the skin surface. The avoidance of hydrocarbon based solvents is generally desirable in medical and personal care applications, and also in paper coating applications where evaporation of organic solvent can be a fire hazard." [col. 5, lines 17-30]

None of these many possible uses describe a controlled release composition containing a protein active agent. Rather, Kosal is directed to a silicone-based pressure sensitive adhesive (PSA) which is designed to adhere to a substrate. In those embodiments in which there is an active agent, the agent is either separate from the PSA and held to the substrate in a conventional manner with the pressure sensitive adhesive, or the active agent is physically mixed with the PSA and adhered to the substrate. As to the latter, Kosal is silent concerning whether the active agent resides in the oil phase or the aqueous phase of the PSA.

Bott et al., the secondary reference, is directed to a topical preparation comprising a continuous silicone phase and a discontinuous phase comprising a hydrophilic carrier and at least one active agent for release from the preparation (see, e.g., paras. [0006], [0033], and [0034]). Unlike Kosal, Bott teaches the use of a *continuous* silicone phase ("silicone matrix") and a *discontinuous* aqueous phase which would be understood by persons skilled in the art to be a water-in-oil composition in which the hydrophilic carrier containing the active agent is dispersed throughout a silicone matrix (see, e.g., para. [0008]). Also, Bott's continuous silicone phase may be a silicone pressure sensitive adhesive (see, para. [0041]).[1]

Thus, in Bott's preparation, a hydrophilic phase containing the active agent and hydrophilic carrier is emulsified with a silicone phase to produce discrete droplets of the aqueous phase dispersed into a continuous silicone phase. The emulsion is then cast and dried, resulting in droplets of the aqueous phase containing the active agent entrapped within the continuous silicone phase. Bott suggests that several mechanisms could be involved in controlling the release of the active agent from the preparation including the addition of hydrophilic agents to the silicone phase or choosing a silicone having a low cross-link density such that the active agent can be released through cracks, pores, or fissures in the silicone phase. See, e.g., paras. [0035] and [0058].

The conclusion of obviousness in the final rejection was based on the argument that one skilled in the art would have been motivated "to combine the teachings of Kosal and Bott et al. and prepare O/W emulsions comprising the hydrophobic phase with silicone PSA taught by Kosal for transdermal delivery of protein active agents" (Action, page 5). The Examiner found "motivation" in Kosal's teaching of providing "controlled tack and lubrication and greater durability, free of hydrocarbon based solvents, and enables holding of the active agent to the skin" (Action, p. 5).

Applicants submit that the supposed "motivation" is not supported by the evidence of record. As noted above, the continuous silicone phase of Bott can be a silicone pressure sensitive adhesive (see, para. [0041] of Bott). Thus, Bott's composition already would possess controlled tack enabling the holding of the active

[1] The tertiary reference, Woodard et al., does not appear to be relied upon in the rejection of claim 72. It is relied upon to support the rejection of other claims on appeal.

agent to the skin. As to "lubrication," the Examiner has not made any cogent argument concerning why such a property would be important, to would not already be inherent in Bott. Finally, as to "greater durability," again, because Bott's composition may include a pressure sensitive silicone adhesive continuous phase, that composition would also be "durable" in the sense of holding the composition to the skin. Thus, all of the Examiner's posited reasons to use Kosal's PSA, already reside in Bott's composition, and there is no motivation for the proposed piecemeal modification of the references' teachings.

***(2) Kosal does not teach or suggest the controlled release of an active agent.***

Applicants disagree with the Examiner's interpretation of Kosal with respect to any teaching concerning controlled release of an active agent. Specifically, applicants' claims are directed to a controlled-release composition and method of delivery. As described in the specification, the term "controlled-release" is defined to mean that the active agent is released in a controlled manner over time ("sustained release") from the composition (see, e.g., Examples 1-8).

Kosal is silent concerning any controlled release properties of his pressure sensitive adhesive composition. That is to be expected, as the Kosal specification is directed primarily to the adhesive composition and its properties, and not to any specific active agents which may be released over time.[2]

The Examiner's comments in the Advisory Action fail to address this important deficiency in Kosal. Nowhere does the Examiner assert that Kosal teaches or suggests that his adhesive provides controlled release properties to any active. To the contrary, the actives in the mascara and sunscreen examples do not release, but rather stay with the adhesive to provide "greater durability" and the like (see, col. 5, lines 20-21). Applicants interpret this statement to mean that the actives stay in place in the adhesive

[2] Applicants note that the Examiner no longer relies upon Kosal's mention, at col. 5, line 18, that the described pressure sensitive adhesives may find use "as release modifying additives for organic pressure sensitive adhesives." As previously explained, that mention must be understood in proper context to be directed to the ability of the adhesive compositions, when blended with other "organic"-based adhesives, to modify the *adhesive release characteristics* of those adhesives which has nothing whatsoever to do with controlling the release of an active agent contained on or within the adhesive.

which is adhered to the skin. While it may be correct to infer that Kosal's mention of the use of the PSA's in mascara and sunscreen compositions is an indication that the actives in the mascara and sunscreen are mixed with the PSA's, there is still total silence on any controlled release functionality. Silence in a reference does not provide evidence of obviousness. *In re Burt*, 148 USPQ 548, 553 (CCPA 1966) (silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow). And, to the contrary, it is reasonable to infer from Kosal's statements concerning "greater durability" that the actives remain within or on the adhesive

Kosal's discussion of the use of an active agent in conjunction with the pressure adhesive composition is limited to the passage at col. 5, lines 19-26, where it is stated that the adhesive may find use (a) in "personal care" applications such as mascara and sunscreen formulations (col. 5, lines 19-23), or (b) as a transdermal drug delivery *patch* or may be used to *hold* a fungicide to the skin surface (col. 5, lines 23-26). However, these are descriptions of using the adhesive composition to secure contact of an active agent against the skin. This is in contrast to the claimed controlled release composition in which the protein active agent is in the continuous hydrophilic phase of an oil-in-water emulsion and is controllably released to act, for example, as a wound debriding agent.

By contrast, Bott teaches placing an active agent in the *discontinuous* phase of a water-in-oil emulsion. Thus, the Bott composition is not only very different from the presently-claimed composition, it also differs significantly from Kosal. Unlike Kosal, Bott teaches the use of a *continuous* silicone phase ("silicone matrix") and a *discontinuous* aqueous phase which would be understood by persons skilled in the art to be a water-in-oil composition in which the hydrophilic carrier containing the active agent is dispersed throughout a silicone matrix (see, e.g., para. [0008]).

Thus, in Bott's preparation, a hydrophilic phase containing the active agent and hydrophilic carrier is emulsified with a silicone phase to produce discrete droplets of the aqueous phase dispersed into a continuous silicone phase. The emulsion is then cast and dried, resulting in droplets of the aqueous phase containing the active agent entrapped within the continuous silicone phase. Bott suggests that several mechanisms could be involved in controlling the release of the active agent from the preparation

including the addition of hydrophilic agents to the silicone phase or choosing a silicone having a low cross-link density. See, e.g., paras. [0035] and [0058]. The two compositions, and their respective mechanisms for controlling the release of active agent, are quite different.

The Examiner's response in the Advisory Action is to argue that "one cannot show nonobviousness by attacking the references individually." However, applicants have not admitted that the references are combinable in the manner proposed by the Examiner or that one skilled in the art would be motivated to do so. Thus, one prong of the attack (to use the Examiner's term) is directed to the Examiner's initial burden of establishing, by evidence and not speculation, that the skilled person viewing Kosal and Bott, and with no knowledge of the claimed invention, would have been motivated to combine their respective teachings. Applicants submit that the evidence of record is deficient and that no prima facie case for the combination of these reference teachings has been made out.

There is a material difference between locating an active agent in an oil-in-water emulsion to control the release of that agent (claimed invention) versus simply holding an active agent against a patient's skin (Kosal). Prolonged contact is not the same as controlled release. The Examiner's attempt to conflate the two ("Kosal's composition is useful in preparations for prolonged or sustained active agent release" [Action at p. 9]) lacks any evidentiary basis. Kosal is silent concerning how long or sustained any release of any active agent might be. And, as discussed above, Kosal appears to suggest that there is no release of any active agent from his PSA.

***(3) Kosal does not address, nor does he solve, any problem relating to the controlled release of an active agent from an adhesive composition.***

The presence of a thickening agent in Kosal's adhesive teaches nothing about the controlled release of an active agent. The assertion by the Examiner at page 11 of the Final Action, that persons skilled in the art would appreciate that Kosal's use of a thickening agent "modifies release of the active agent, e.g., a fungicide," is speculation, unsupported by any evidence. Nothing in Kosal teaches this. To the contrary, Kosal simply states that the pressure sensitive adhesive will "hold" the active agent to the skin.

There is absolutely no statement in any way relating the presence of an optional thickening agent to the control of the release of an active agent.

With respect to the Examiner's comments in the Advisory Action, applicants respectfully submit that it is the Examiner who misses the point of the argument. Any assertion about what a skilled person would appreciate must be supported by evidence in the record, not speculation.

Further, the statement at page 11 of the Final Action that, "absent evidence, it is not seen that the composition of Kosal et al. prepared by phase inverting the composition of Bott et al. would result in a different mechanism, not rate, of release control," contains both factual and legal error. Initially, it is not an applicant's burden to provide evidence to negate obviousness; to the contrary, it is the Office's legal burden to establish evidence that supports the conclusion of obviousness. And, the facts in this instance are explicit and clear. Bott states that the possible mechanisms for release of the active agent from the water-in-oil composition are the creation of "pores, crevices, cracks, or fissures within the silicone matrix," or the presence of hydrophilic agents in the silicone phase, or the choice of a silicone having a low crosslink density (paragraphs [0035] and [0058]). These are certainly statements of different *mechanisms* for release of the active agent than that described by applicants. Kosal's only description of the use of an active, as discussed above, is to use the pressure sensitive adhesive to cover an active and hold it against the surface of the skin or to mix an active into the PSA for the purpose of holding the active in place. Thus, the facts (as opposed to speculation) are that Bott teaches a different mechanism, and Kosal is silent. These facts do not support the Examiner's conclusion of obviousness; rather, they undercut it.

The Examiner's assertion in the Advisory Action that "the MPEP is silent as to the Office's burden to provide evidence that supports obviousness" is simply wrong. As explicitly stated in §2142 of the MPEP,

> The legal concept of prima facie obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Saunders*, 444 F.2d 599, 170 USPQ 213 (CCPA 1971); *In re Tiffin*, 443 F.2d 394, 170 USPQ 88 (CCPA 1971), amended, 448 F.2d 791, 171 USPQ 294 (CCPA 1971); *In re Warner*, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). The

> examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness.

Applicants respectfully submit that, in this context, "factual support" and "evidence" are synonymous.

***(4) Applicants are not attacking the references individually.***

The legal evidentiary burden is on the Office to establish facts that support the conclusion that not only would one skilled in the art be motivated to combine references teachings, but also that there would be a reasonable expectation of success in doing so. Applicants submit that that evidentiary burden has not been carried because the reference teachings are not combinable in the manner proposed, and even if combined would not result in the claimed invention.

The Examiner's asserted "motivation" for combining reference teachings involves Kosal's statements regarding the properties of the pressure sensitive adhesive (Action at page 5). None of those statements supports the conclusion that the skilled person would be motivated to combine the reference teachings as none of these properties relate to the controlled release of an active agent from the composition.

(a) "controlled tack and lubrication" – This statement relates to the use of Kosal's pressure sensitive adhesive in paper coatings for adhesive labels and envelope sealing strips (col. 5, lines 14-17). These properties have nothing to do with the controlled release of any active agent.

(b) "greater durability" – This statement is with respect to "personal care compositions" (col. 5, lines 19-20) such as "mascara" and "sunscreen formulations" and their "durability" on the skin of a user. These properties have nothing to do with the controlled release of an active agent.

(c) "free of hydrocarbon based solvents" – This is taught to be "desirable," not required, (col. 5, lines 27-30), for some uses of the adhesive. Again, there is no teaching that this property has any effect on the release of an active agent from the composition.

(d) "holding of the active agent to the skin surface" – This would be an expected property of a pressure sensitive adhesive. Again, however, the terms "prolonged" and "controlled release" have been equated when the record is clear that they are not. As discussed above, the two words have different meanings and would be so understood by persons skilled in this art.

(e) Kosal's oil-in-water emulsion results from the inversion of a water-in-oil emulsion – In general, this is a conventional method for making an oil-in-water emulsion. However, the fact that Bott is a water-in-oil emulsion provides no motivation "to combine Kosal and Bott et al" (Final Action at page 11). Applicants fail to see the factual basis for any motivation for Kosal to use Bott's emulsion, especially where Kosal is directed to a pressure sensitive adhesive and Bott, primarily, is not. While Kosal does teach a phase inversion technique, that technique is performed with no active agent in the aqueous phase because Kosal either has no need for any active agent, or mixes in the active agent after forming the emulsion.

When stripped of all speculation, the rejection is that a skilled person, without knowledge of the claimed invention, would look to a pressure sensitive adhesive composition (Kosal) which does not even address the problem of providing the controlled release of a protein active agent, and then modify that pressure sensitive adhesive composition by substituting a water-in-oil emulsion (Bott) that does use a protein active agent and inverting it into an oil-in water emulsion to form a pressure sensitive adhesive that contains a protein active agent. The rejection is based on speculation and prohibited hindsight.

Applicants submit that this rejection is flawed both factually and legally for the many reasons discussed above. Independent claim 72 is patentable over Kosal and Bott. As for dependent claims 74-86, applicants submit that as they depend directly or indirectly from patentable independent claim 72, those claims are patentable for the same reasons that claim 72 is patentable as discussed in detail above. Further, as claim 90 recites a method of using the composition of claim 72, claim 90 is patentable for the same reasons that claim 72 is patentable.

Claims 87-88

With respect to claims 87-88 which are directed to a multi-layer dressing, the Examiner has cited Woodard et al. (US 4655767) for its teaching of a transdermal drug delivery device having multiple layers. The rejection does not explicitly provide a motivation for combining Woodard with the other reference teachings other than to allude to the rejection of claim 72 over Kosal and Bott and the fact that Woodard evidences that three-layer transdermal drug delivery devices were known in the art (Final Action, p. 6 and comments in the Advisory Action). Nor were any specific modifications or substitutions proposed by the Examiner for any of the compositions of Kosal or Bott or the construction of Woodard.

It is apparent that Kosal's adhesive could be used as adhesive layer 22 in Woodard, but that substitution does not meet the claims. Applicants also note that in Woodard, the active agent (drug) is located in elastomer layer 20, not adhesive layer 22. Based on the rejection of claim 72, from which claims 87-88 depend, it was proposed to include the active agent of Bott in the pressure sensitive adhesive of Kosal. But, so modifying those references would render layer 20 in Woodard superfluous. Applicants also note that while Woodard teaches that the device 10 is adhered to a patient's skin, nowhere in the passage at col. 3, lines 13-27, is it stated that such pressure causes the "drug-impregnated elastomer layer" to come into contact with the skin as alleged by the Examiner (Final Action at page 13). As best understood, even if the reference teachings were combinable in the manner proposed by the Examiner (which manner has certainly not been made clear in any of the Actions), the construction would be different than the subject matter of claims 87-88.

Claim 89

Finally, with respect to the rejection of claim 89, it is clear that Kosal does not teach or suggest a controlled release layer free of water. Indeed, as discussed above, Kosal is silent concerning any controlled release of an active agent that his adhesive may or may not include. And, while Bott teaches an embodiment using a dry patch, again, Bott teaches a water-in-oil emulsion, not an oil-in-water emulsion. The reference teachings are not combinable in the manner proposed by the Examiner. Even if those

teachings were to be combined, the claimed subject matter would not result because Bott, which is the only reference that relates to the controlled release of an active agent, explicitly teaches one to use a water-in-oil emulsion.

***Conclusion***

The Board is requested to reverse the rejection of claims 72 and 74-91 in their entirety.

Respectfully submitted,

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CLAIMS APPENDIX

72. A controlled-release composition for topical application to a substrate, said composition comprising: an oil-in-water emulsion substantially free of lipophilic solvent wherein the oil-in-water emulsion has a hydrophilic phase comprising a protein as an active agent, water, and a carrier, and a hydrophobic phase comprising a silicone component.

74. A controlled-release composition as set forth in claim 72 further comprising a surfactant between said hydrophilic and hydrophobic phases.

75. A controlled-release composition as set forth in claim 72 wherein said carrier is selected from the group of glycerin, propylene glycol, polyethylene glycol, poloxamer, alcohol, polyhydric alcohol, water, polyvinyl alcohol, polyvinylpyrrolidone, and combinations thereof.

76. A controlled-release composition as set forth in claim 72 wherein said carrier is in solution with said water.

77. A controlled-release composition as set forth in claim 72 wherein said protein is an enzyme.

78. A controlled-release composition as set forth in claim 77 wherein said enzyme is selected from the group of natural enzymes, synthetic enzymes, engineered enzymes, and combinations thereof.

79. A controlled-release composition as set forth in claim 77 wherein said enzyme is selected from the group of oxidoreductases, transferases, isomerases, ligases, hydrolases, cutinases, oxidases, reductases, hemicellulases, esterases, pectinases, lactases, peroxidases, laccases, catalases, and combinations thereof.

80. A controlled-release composition as set forth in claim 77 wherein said enzyme

comprises Protease A, Protease B, or LG12.

81. A controlled-release composition as set forth in claim 74 further comprising a dispersing agent for dispersing said protein.

82. A controlled-release composition as set forth in claim 81 wherein said dispersing agent comprises a silicone-based surfactant different from said surfactant.

83. A controlled-release composition as set forth in claim 72 wherein said silicone component is selected from the group consisting of a silicone gum, a silicone rubber, a silicone elastomer, a silicone resin, high molecular weight silicones, silicone emulsions, and combinations thereof.

84. A controlled-release composition as set forth in claim 72 wherein said silicone component comprises a pressure sensitive adhesive.

85. A controlled-release composition as set forth in claim 84 wherein said pressure sensitive adhesive comprises the reaction product of; a hydroxy endblocked polydimethylsiloxane polymer, and a hydroxy functional silicate resin.

86. A controlled-release composition as set forth in claim 85 wherein said hydroxy functional silicate resin is further defined as a trimethylsiloxy and hydroxy endblocked silicate resin.

87. A controlled release composition as set forth in claim 72 in the form of a multi-layer dressing for topical application to a substrate, said dressing comprising: (A) a controlled-release layer formed from said controlled-release composition of claim 72; (B) an adhesive layer disposed adjacent said controlled-release layer for adhering said

dressing to the substrate; and (C) an additional layer selected from the group of a backing layer, a cushioning layer, an absorbent layer, a second adhesive layer, and

combinations thereof.

88. A controlled release composition as set forth in claim 87 wherein said controlled-release layer is adjacent the substrate and said additional layer is disposed adjacent said adhesive layer spaced from said controlled-release layer.

89. A controlled release composition as set forth in claim 87 wherein said controlled-release layer is dry in said dressing such that said controlled-release layer is free of water after said controlled-release layer is formed by said controlled-release composition.

90. A method of delivering the controlled release composition of claim 72 to a substrate comprising:

applying the controlled release composition to a dressing; and

applying the dressing to the substrate.

91. The controlled-release composition as set forth in claim 72 wherein said protein is selected from the group of antibodies, polypeptides, peptides, hormones, cytokines, growth factors, biological modulators, and combinations thereof.

EVIDENCE APPENDIX

NONE

RELATED PROCEEDINGS APPENDIX

NONE